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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/596,444	06/19/2000	Wei Huang	LJL 354B	4000

7590 10/04/2005

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EXAMINER	
LAM, ANN Y	
ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 10/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action Summary	Application No. 09/596,444	Applicant(s) HUANG ET AL.	
	Examiner Ann Y. Lam	Art Unit 1641	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *50-59 and 61-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50-59 and 61-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 22, 2005 has been entered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 50-52, 54, 55, 57, 59 and 62-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nikiforov, 6,287,774, in view of Zhou, et al. "Detection and Sequencing of Phosphopeptides Affinity Bound to Immobilized Metal Ion Beads by Matrix-Assisted Laser Desorption/Ionization Mass Spectrometry", American Society for Mass Spectrometry, April 2000, Vol. 11, pp. 273-282.

Nikiforov discloses the invention substantially as claimed.

As to claim 50, Nikiforov discloses a method of detecting addition or removal of a phosphate group to or from a substrate (col. 13, lines 40-42, and lines 47-50), comprising:

contacting a luminescent peptide (i.e., fluorescently labeled phosphorylatable substrate 302, col. 13, line 20) with a binding partner (i.e., polycation, col. 13, line 26) that binds specifically to the peptide only if the peptide is phosphorylated (col. 13, lines 29-30), wherein the binding partner includes an entrapped metal (col. 13, line 35) that selectively binds to phosphorylated peptides, and wherein the peptide is a substrate (302, col. 13, line 20) for an enzyme (i.e., kinase enzyme 306, col. 13, line 20) that catalyzes addition or cleavage of a phosphate group to or from a protein (col. 13, lines 19-21),

and measuring luminescence polarization from the luminescent peptide (col. 6, lines 1-5), wherein the amount of measured luminescence polarization can be related to the extent of binding between the luminescent peptide and the binding partner (col. 6, lines 1-12.)

However, Nikiforov does not list gallium as an example of the entrapped metal. (Rather Nikiforov teaches that the entrapped metal is a multivalent metal cation that may for example be Fe^{3+}(see col. 13, lines 32-39.)

Zhou et al. however teach the motivation to use gallium as the metal ion. Zhou et al. teach that immobilized metal ions, such as Fe^{3+} bind with high specificity to phosphoproteins and peptides, and that Ga^{3+} (i.e., a gallium cation) has been

discovered as having better selectivity for the phosphopeptides (page 274, left column, last paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize a gallium cation as taught by Zhou et al. as the entrapped metal in the Nikiforov invention because Zhou et al. teaches that gallium has an advantage over other cations such as Fe^{3+} because it has better selectivity for phosphopeptides, which would result in more accurate results in the Nikiforov invention. (The Office also notes that both Nikiforov and Zhou et al. lists Fe^{3+} as an example of a metal cation that bind to phosphopeptides (see Nikiforov, col. 13, lines 35-42, and Zhou et al. page 274, left column, last paragraph) and that Zhou et al. further lists Ga^{3+}. Thus, at the very least, Zhou et al. teach that Fe^{3+} and Ga^{3+} are functional equivalents as metal cations that bind to phosphoproteins.)

As to the following claims, Nikiforov discloses the limitations as follow.

As to claim 51, the step of correlating the measured luminescence polarization with kinase activity is disclosed (col. 6, lines 1-12, and col. 7, lines 27-31, and col. 13, lines 19-26.)

As to claim 52, phosphatase activity is determined (col. 13, lines 59-66).)

As to claim 54, the step of measuring luminescence polarization includes illuminating the sample with polarized light (col. 5, line 13.)

As to claim 55, the luminescent peptide is exposed to the enzyme in a reaction mixture to catalyze phosphorylation or dephosphorylation of the peptide (col. 13, line 19-21).

As to claim 57, the binding partner binds specifically to a phosphorylated protein substantially without regard to the particular amino acid sequence of the protein (col. 13, lines 29-21.)

As to claim 59, the method includes contacting the luminescent peptide and the enzyme with a candidate modulator (phosphate 304, col. 13, line 21), prior to the step of measuring luminescence polarization (col. 13, lines 19-21, and lines 38-46.)

As to claim 62, the step of exposing [the peptide to the enzyme] precedes the step of contacting [the peptide to the binding partner/metal cation], (col. 13, lines 19-21 and lines 25-26.)

As to claim 63, the step of exposing catalyzes a reaction having an end point, and wherein the step of measuring is performed at different times during the reaction before the end point (see col. 24, lines 56-67.)

As to claim 64, the step of exposing catalyzes a reaction having an end point, and wherein the step of measuring is performed at different times during the reaction before the end point (see col. 24, lines 56-67.)

As to claim 65, the step of measuring is performed after the step of contacting without separation of bound and unbound species of the luminescent peptide (col. 13, lines 25-26, lines 44-46, and col. 24, lines 26-56.)

2. Claim 56 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Nikiforov**, 6,287,774, in view of **Zhou, et al.** "Detection and Sequencing of Phosphopeptides Affinity Bound to Immobilized Metal Ion Beads by Matrix-Assisted

Laser Desorption/Ionization Mass Spectrometry", American Society for Mass Spectrometry, April 2000, Vol. 11, pp. 273-282, as applied to claims 50 and 55 above, and further in view of **de Sauvage et al.**, 6,022,708.

Nikiforov in view of Zhou et al. disclose the invention substantially as claimed (see above), except for the assay being a competitive assay, including the step of catalyzing formation of unlabelled phosphorylated protein in the reaction mixture to competitively bind to the binding partner.

De Sauvage however teaches the motivation to perform the Nikiforov direct assay format in a competitive assay format.

De Sauvage discloses a method of detecting addition or removal of a phosphate group to or from a substrate (column 32, lines 56-58), comprising contacting a luminescent peptide (i.e., the "substrate", column 32, line 58) with a binding partner (i.e., "antibody", column 33, line 11) that binds specifically to the peptide only if the peptide is phosphorylated (column 33, lines 11-12), or only if the peptide is not phosphorylated, wherein the peptide is a substrate (i.e., "kinase substrate", column 32, line 53) for an enzyme that catalyzes addition or cleavage of a phosphate group to or from a protein (column 32, lines 53-55.)

De Sauvage discloses that various diagnostic assay techniques known in the art may be used, such as competitive binding assay, direct and indirect sandwich assays (column 28, lines 63-64.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize competitive binding assay as taught by de Sauvage in the

Nikiforov assay method because de Sauvage teaches that competitive assays are an obvious alternative to the direct assay of Nikiforov to detect addition or removal of phosphate groups from a substrate.

3. Claims 53, 58 and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Nikiforov**, 6,287,774, in view of **Zhou, et al**. "Detection and Sequencing of Phosphopeptides Affinity Bound to Immobilized Metal Ion Beads by Matrix-Assisted Laser Desorption/Ionization Mass Spectrometry", American Society for Mass Spectrometry, April 2000, Vol. 11, pp. 273-282, and applied to claim 50 above, and further in view of in view of **Fuller**, 5,424,190.

Nikiforov in view of Zhou et al. disclose the invention substantially as claimed (see above). Moreover, Nikiforov discloses examples of binding pairs substrates and enzymes (col. 7, lines 19-31.) However, Nikiforov does not disclose a stop solution including a chelator, and that the steps of contacting and measuring are performed in a microplate well.

Fuller teaches a stop solution such as EDTA which comprises a chelator useful to inactivate enzymes prior to analysis of the product of the enzymatic reagents (col. 1, lines 13-15 and 24-40, and col. 2, line 18, and lines 30-34.)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to provide EDTA as a stop solution as taught by Fuller in the Nikiforov enzymatic assay method because Fuller teaches that such solution is conventionally used to inactive enzymes desirable for stopping a reaction in an

enzymatic assay providing the advantage of facilitating subsequent analysis of the product of the enzymatic reagents in the Nikiforov assay.

Fuller also teaches use of a microtiter plate (which are known to have wells) for performing the assay reactions (col. 2, lines 36-38.)

It would have been obvious to utilize a microplate well as taught by Fuller in the Nikiforov assay method as a well known and conventional means to hold reagent and stop solutions as would be desirable for performing an assay.

4. Claim 61 is rejected under 35 U.S.C. 103(a) as being unpatentable over **Nikiforov**, 6,287,774, in view of **Zhou, et al**. "Detection and Sequencing of Phosphopeptides Affinity Bound to Immobilized Metal Ion Beads by Matrix-Assisted Laser Desorption/Ionization Mass Spectrometry", American Society for Mass Spectrometry, April 2000, Vol. 11, pp. 273-282, and applied to claims 50, 55 and 59 above, and further in view of in view of **Maxfield Wilson et al.**, 5,776,487.

Nikiforov in view of Zhou et al. disclose the invention substantially as claimed (see above), except for the particular order of carrying out the steps as recited in claim 61. That is, Nikiforove and Zhou et al. do not teach that the step of contacting the enzyme with the candidate modulator (phosphate) is performed before the step of exposing the luminescent peptide to the enzyme. (Rather, Nikiforov only discloses that the peptide (substrate) is contacted with the enzyme in the presence of the phosphate (304) and does not disclose any particular order.)

Maxfield Wilson et al. however teaches adding reagents in an assay simultaneously or sequentially for binding of the reagents (col. 5, lines 39-45.) It would have been obvious to one of ordinary skill in the art at the time the invention was made to provide the Nikiforov reagents sequentially, such as contacting the enzyme with the phosphate before contacting the enzyme with the luminescent peptide because Maxfield Wilson et al. teach that simultaneously or sequentially contacting reagents equally provide the function of allowing binding between the reagents, such as the Nikiforov reagents.

Response to Arguments

Applicant's arguments with respect to the above rejected claims have been considered but are moot in view of the new ground(s) of rejection. (Zhou et al. provides a much more specific motivation to combine the teachings, as described above.)

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ann Y. Lam whose telephone number is 571-272-0822. The examiner can normally be reached on M-Sat 11-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

A.L.

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09/30/05